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ORIGINAL ARTICLE

# Periodontal inflamed surface area and C-reactive protein as predictors of HbA1c: a study in Indonesia

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**Abstract** Periodontitis may exert an infectious and inflammatory burden, evidenced by increased C-reactive protein (CRP). This burden may impair blood glucose control (HbA1c). The aim of our study was to analyze whether periodontitis severity as measured with the periodontal inflamed surface area (PISA) and CRP predict HbA1c levels in a group of healthy Indonesians and a group of Indonesians treated for type 2 diabetes mellitus (DM2). A full-mouth periodontal examination, including probing pocket depth, gingival recession, clinical attachment loss, plaque index and bleeding on probing, was performed in 132 healthy Indonesians and 101 Indonesians treated for DM2. Using these data, PISA was calculated. In addition, HbA1c and CRP were analyzed. A validated questionnaire was used to assess smoking, body mass index (BMI), education and medical conditions. In regression analyses, it was assessed whether periodontitis severity and CRP predict HbA1c, controlling for confounding and effect modification (i.e., age, sex, BMI, pack years, and education). In healthy Indonesians, PISA and CRP predicted HbA1c as did age, sex, and smoking. In Indonesians treated for DM2, PISA did not predict HbA1c. Periodontitis may impair blood glucose regulation in healthy Indonesians in conjunction with elevated CRP levels. The potential effect of periodontitis on glucose control in DM2 patients may be masked by DM2 treatment. Clinical relevance: periodontitis may impair blood glucose control through exerting an inflammatory and infectious burden evidenced by increased levels of CRP.

**Keywords** Periodontitis · Periodontal inflamed surface area/PISA · HbA1c · Type 2 diabetes mellitus

Hendri Susanto and Willem Nesse equally contributed to this study.

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## Introduction

Periodontal inflamed surface area (PISA) quantifies the amount of inflamed periodontal tissue and is supposed to quantify the inflammatory and infectious burden resulting from periodontitis [1]. Periodontitis may cause an inflammatory burden through the production of local inflammatory mediators entering the systemic circulation. This inflammatory burden is evidenced by increased serum C-reactive protein (CRP) levels found in patients suffering from periodontitis [2–7].

Periodontitis may also cause an infectious burden through bacteria and their products entering the systemic circulation. This burden may endanger overall health by for example causing atherosclerosis [8] and cardiovascular diseases [9].

Circulating oral bacteria and lipopolysacharides are also able to stimulate hepatocytes to secrete CRP [10–12]. Thus, increased levels of CRP associated with periodontitis may be considered as a common pathway for both the inflammatory and infectious burden resulting from periodontitis.

The high levels of CRP accompanying periodontitis, may lead to insulin resistance and thereby to poor control of blood glucose in type 2 diabetes mellitus (DM2) and healthy subjects [13–16] resulting in increased levels of glycated hemoglobin (HbA1c) [17, 18]. Accordingly, high levels of CRP are correlated with increased HbA1c levels in DM2 patients [19, 20]. Increased CRP levels have also been associated with an increased risk of cardiovascular disease (CVD) in DM2 patients, the major cause of the increased mortality in DM2 patients [21, 22].

Given the importance of blood glucose control in preventing CVD in DM2 patients, relatively few studies assessed whether the specific combination of periodontitis and CRP as a reflection of inflammatory burden, predict HbA1c levels [23, 24]. Furthermore, no study has investigated this issue in Indonesia while this country is in the top ten of countries with the highest prevalence of DM (at 5.7%) in the world in 2005. It has been estimated that by the year 2030, the prevalence of DM in Indonesia will be about 10%, corresponding with 20 million DM patients [25, 26]. In addition to a high DM prevalence, a high prevalence of periodontitis has been reported in Indonesia [27]. Finally, depending on the definition used, our previous study showed that Indonesian DM2 patients have a prevalence of periodontitis at 72% to 93% and an increased severity of periodontitis [28]. Therefore, the aim of this study was to assess whether periodontitis severity, as measured with the PISA method and CRP predict HbA1c levels in healthy Indonesians and Indonesian treated for DM2 patients.

## Materials and methods

The participants in this study were recruited from three different sites, namely (1) the Internal Medicine Department Dr. Sardjito Hospital, Yogjakarta, 2) Prof. Soedomo Dental Hospital, Faculty of Dentistry, Gadjah Mada University, Yogjakarta, and 3) Diabetes Center of Jogjakarta International Hospital, Yogjakarta, Indonesia. All participants had to be aged ≥18 years and had to have ≥8 remaining teeth. The latter inclusion criteria was proposed prior to commencing the study since current inflammatory burden posed by periodontitis requires the presence of at least a minimum number of teeth affected by periodontitis. This study was approved by the Ethical Committee for Research of the Medical Faculty of Gadjah Mada University, Yogjakarta, Indonesia.

All participants completed a validated general health assessment questionnaire [29, 30] to check for other medical conditions that might be a risk factor for periodontitis. Information on age, gender, height and weight (for body mass index (BMI) calculation), education, and smoking were obtained from each participant.

All participants underwent a periodontal examination including periodontal probing pocket depth (PD), gingival recession, plaque score, and bleeding on probing (BOP) measurements by trained and calibrated examiners (HS, YHR, and EH). All measurements were performed on all teeth, on six sites per tooth using a manual periodontal color-coded standard probe (Dentsply™, London, UK).

Clinical attachment loss (AL) was defined as the distance from the cementoenamel junction to the bottom of the pocket/sulcus and calculated as the mathematical sum of the PD and gingival recession measurements [31]. Measurements were made in millimeters and were rounded off to the nearest millimeter. BOP was recorded as either present or absent within 30 s of probing at six sites per tooth. Plaque score was defined as being present or absent at six points on each tooth [32]. The number of missing teeth was also recorded.

Periodontitis extent and severity were operationalized using a variety of methods, all of which are currently used in literature studying the association between periodontitis and other diseases. All measurements were calculated using conventional clinical measurements obtained during the full-mouth periodontal examination (HS and WN). The number of sites with probing PD of ≥4, ≥5, and ≥6 mm, the numbers of sites with clinical AL of ≥3, ≥4, ≥5, and ≥6 mm, mean PD, mean AL [33], and the percentage of sites with BOP were calculated. Additionally, a recently introduced measure of periodontitis severity, the PISA [1] was calculated, PISA quantifies the amount of inflamed periodontal tissue, and it is suggested that PISA thereby quantifies the inflammatory burden exerted by periodontitis [1].

Finally, all participants underwent a venapuncture to obtain a blood sample. Both blood glucose (fasting blood glucose), determined by glucose oxidase enzymatic method, and glycosilated/glycated hemoglobin (HbA1c) values, determined using low pressure cation ion exchange chromatography (DIASTAT™, Bio-Rad, USA), were determined for all participants. Additionally, CRP, determined by a high-sensitivity chemiluminescent immunometris assay (Immulite 2000™, Diagnostic Products Corp., Los Angeles, CA, USA), were determined for all participants.

### Statistical analysis

Differences in periodontitis severity between DM2 and healthy subjects were analyzed first using univariate

analyses (independent sample *t* test, Mann–Whitney *U* test, or Chi-square test as appropriate). Likewise, differences in potential predictors of periodontitis (age, gender, BMI, education, smoking, plaque score, number of teeth, ethnicity, and other medical conditions) between DM2 patients and healthy subjects were tested for significance using univariate analyses. Since periodontitis severity was operationalized in 12 different ways, significance level $\alpha$ of 0.05 was corrected for multiple comparisons according to the Bonferroni–Holm method.

To assess periodontitis and CRP as potential predictors of HbA1c in subjects with and without DM2, a multiple linear regression analysis was performed, using a backward stepwise method. HbA1c was the dependent. As independent variables, i.e., predictors of HbA1c: age, sex, BMI, pack years, education, CRP, and all measures of periodontitis severity. The latter were introduced in the model one by one. Statistics were calculated using SPSS 16.0.

## Results

In a total of 101 participants, 40 men and 61 women, with a mean age of 54 years treated for DM2, diagnosed according to World Health Organization criteria [34] were included (Table 1). Most of the participants were of Javanese origin (93.0%). The mean BMI in this group was 25.5, labeling them as being overweight according to the World Health Organization classification (overweight—BMI, 23–27.5) [35]. The DM2 patients had an average of 24 teeth with a mean plaque score of 91% (Table 2). The mean HbA1c in the DM2 group was 8.9%. In addition, a total of 132 healthy controls was enrolled, 34 men and 98 women, with a mean age of 48 years. Again, the healthy subjects were mainly of Javanese origin (90%) and were on average ranked as being overweight according to the BMI index for Asian populations (BMI, 24.4) [35]. The healthy subjects had an average of 26 teeth and a mean plaque score of 93%. The average HbA1c level of this group was 5.5% (below 6.5% classified as healthy/non diabetic).

The severity of periodontitis was significantly higher in participants with DM2 when compared to controls, again independent of the method used to operationalize periodontitis severity (Table 2). In the DM2 patients, none of the measures of periodontitis severity predicted HbA1c. Only SES ($\beta$=−0.752; 95% CI=−1.345 to −0.158) was a predictor of HbA1c, ($r^2$ of 6.0%; data not shown). By contrast, in healthy Indonesians, PISA ($\beta$=0.0004; 95% CI=0.00004-0.00076) was a predictor of HbA1c together with age, sex, smoking and CRP, ($r^2$=21%) in the model (Table 3).

**Table 1** Characteristics of the participants

| Variables | DM2 ($n$=101) | Healthy controls ($n$=132) | $p$ value |
|---|---|---|---|
| Demography | | | |
| Age (years) mean (SD) | 54.4 (10.7) | 47.9 (10.1) | <0.001 |
| Smoking (pack year) median (IQR)[b] | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.109 |
| BMI (kg/m$^2$) mean (SD) | 25.5(4.2) | 24.4 (3.8) | 0.054 |
| Java origin ($n$ (%))[a] | 94 (93%) | 119 (90%) | 0.431 |
| Gender ($n$ (%))[a] | | | <0.05 |
| Male | 40 (40%) | 34 (26%) | |
| Female | 60 (60%) | 98 (74%) | |
| Education ($n$ (%))[a] | 2.18 (0.79) | 2.13 (0.77) | 0.662 |
| Low (6–9 years) | 32 (24%) | 24 (23%) | |
| Middle (9–12 years) | 51 (39%) | 34 (34%) | |
| High (12–17 years) | 49 (37%) | 43 (43%) | |
| Hypertension (yes) ($n$ (%))[a] | 26 (26%) | 24 (18%) | 0.164 |
| Medication ($n$ (%)) | | | |
| Sulfonylurea | 55 (54%) | NA | NA |
| Insulin | 41 (41%) | NA | |
| Metformin | 37 (37%) | NA | |
| Acarbose | 33 (33%) | NA | |
| Laboratory serum markers | | | |
| HbA1c (%) mean (SD) | 8.9 (2.4) | 5.5 (0.4) | <0.001 |
| CRP (mg/l) median (IQR)[b] | 2.8(1.6–7.0) | 1.1 (0.6–2.3) | <0.001 |

$p$ values were Bonferroni–Holm corrected. A $p$ value of <0.05 was considered statistically significant

$p$ probability, *BMI* body mass index, *CRP* C-reactive protein, *DM2* diabetes mellitus type 2, *HbA1c* glycated hemoglobin, *IQR* interquartile range, $n$ number of participants, *NA* not applicable, *SD* standard deviation, low, elementary and junior school (education), *middle* high school (education), *high* university (education)

[a]Result of Chi-square test

[b]Result of Mann–Whitney *U* test; other results are the results of the independent samples *t* test

**Table 2** Periodontal status of healthy controls and DM2

| Variables | Healthy controls ($n$=132) | DM2 ($n$=101) | $p$ value |
|---|---|---|---|
| Periodontal prevalence ($n$ (%))[a] | | | |
| PD (≥4 mm) and AL (≥3 mm) | 89 (67%) | 89 (88%) | <0.001 |
| PD (≥5 mm) AL (≥2 mm) | 43 (33%) | 67 (66%) | <0.001 |
| Periodontal severity (median (IQR))[b] | | | |
| PISA ($mm^2$) | 83.9 (35.2–206.4) | 170.4 (91.5–392.6) | <0.017 |
| AL (mm) | 1.8 (1.7–2.3) | 2.4 (2.0–3.4) | <0.001 |
| PD (mm) | 1.7 (1.6–1.9) | 1.9 (1.7–2.4) | <0.001 |
| Number of sites (median (IQR))[b] | | | |
| AL (≥3 mm) | 30.0 (17.0–47.0) | 54.0 (32.50–74.50) | <0.001 |
| AL (≥4 mm) | 5.0 (1.0–15.8) | 25.0 (9.0–48.0) | <0.001 |
| AL (≥5 mm) | 1.0 (0.0–4.8) | 13.0 (2.0–31.50) | <0.001 |
| AL (≥6 mm) | 0.0 (0.0–1.0) | 4.0 (0.0–19.5) | <0.001 |
| PD (≥4 mm) | 2.0 (0.0–4.0) | 6.0 (2.0–18.0) | <0.001 |
| PD (≥5 mm) | 0.0 (0.0–1.0) | 2.0 (0.0–8.0) | <0.001 |
| PD (≥6 mm) | 0.0 (0.0–0.0) | 1.0 (0.0–3.0) | 0.001 |
| BOP ($n$ (%)) | 9.0 (4.0–20.0) | 18.0 (10.0–31.5) | <0.001 |
| Mean (SD) | | | |
| Plaque score (%) | 93% (8.5) | 91% (7.9) | 0.059 |
| Number of teeth | 25.7 (4.7) | 23.6 (6.2) | 0.005 |

$p$ values were Bonferroni–Holm corrected. A $p$ value of <0.05 was considered statistically significant

$p$ probability, *BOP* bleeding on probing, *AL* clinical attachment loss, *DM2* diabetes mellitus type 2, *IQR* interquartile range, $n$ number of participants, *PISA* periodontal inflamed surface area, *PD* probing pocket depth, *SD* standard deviation

[a]Result of Chi-square test

[b]Result of Mann–Whitney $U$ test; other results are the results of the independent samples $t$ test

## Discussion

This study showed that PISA is a predictor of HbA1c, in conjunction with CRP, age, sex, and smoking, in healthy Indonesians. Thus, periodontitis may play a role in inducing impaired blood glucose control. Indeed, there is evidence that periodontitis may induce insulin resistance [18]. It is thought that periodontitis exerts an inflammatory and infectious burden as evidenced by increased levels of CRP [3, 5, 6] which may increase HbA1c levels [19, 20, 36]. Accordingly, PISA predicted HbA1c together with CRP.

**Table 3** Results of the multiple linear regression analysis healthy control group

| Model predictors | $\beta$ | $p$ value of $\beta$ | $R^2$ | 95% confidence interval of $\beta$ |
|---|---|---|---|---|
| Model | | | 0.21 | |
| PISA ($mm^2$)[a] | 0.0004 | <0.05 | | 0.00004 to 0.00076 |
| Age (year) | 0.0105 | 0.001 | | 0.00431 to 0.01674 |
| Male/female (1/0) | −0.1378 | 0.08 | | −0.29170 to 0.01595 |
| Smoking (pack year) | 0.0086 | 0.07 | | −0.00074 to 0.01805 |
| CRP (mg/l) | 0.0212 | 0.06 | | −0.00093 to 0.04343 |
| Constant | 4.9591 | <0.001 | | 4.62706 to 5.29121 |

A $p$ value of <0.05 was considered statistically significant. Dependent variable—HbA1c; independent variables: PISA, age, sex, and smoking/pack years. Constant

$p$ probability, $\beta$ unstandardized coefficient, *HbA1c* glycated hemoglobin, periodontal inflamed surface area, *CRP* C-reactive protein

[a] Other measures of periodontitis severity were not predictors of HbA1c

It is striking that out of the various methods to operationalize periodontitis severity, only the PISA emerged as a predictor of HbA1c. The other methods for determining the severity and extent of periodontitis did not contribute significantly to a model that predicts HbA1c. It may be that the PISA is a predictor of HbA1c because it reflects the amount of inflamed periodontal tissue, thereby predicting both infectious and inflammatory burden more accurately than other methods used to operationalize periodontitis [1, 18].

In Indonesian DM2 patients, no measure for periodontitis severity predicted HbA1c. The observed differences between DM2 patients and healthy Indonesians may be explained as follows. First, almost all DM2 patients used a combination of medication to control blood sugar, drugs that healthy Indonesians obviously did not take [37]. Use such medication may mask an effect of periodontitis on the HbA1c level in DM2 patients. Second, DM2 patients may have dietary restrictions, e.g., avoiding sugar rich foods. Such a diet may impact blood sugar and may mask an affect of periodontitis on HbA1c level.

Previously, a dose–response relationship was observed between PISA and HbA1c in DM2 patients from the Caribbean island, Curacao [18]. Additionally, an increased HbA1c was observed to be associated with increased severity of periodontitis [38]. Moreover, it has been

reported that periodontal treatment leads to improvement of glycemic control in DM2 patients [39]. These findings appear to be in sharp contrast with the findings in this study, i.e., PISA is not a predictor of HbA1c in a group of Indonesian DM2 patients. The difference between the current study and the study in Curacao [18] could be explained by differences in populations. First, substantial differences were observed in the frequency of antidiabetics used between DM2 from Indonesia and Curacao. Acarbose (33% vs. 5%), insulin (41% vs. 21%), and sulfonylurea (54% vs. 35%) were used more often in DM2 patients from Indonesia, while metformin 37 vs. 67% was used more often in DM2 patients from Curacao. Additionally, 16% of DM2 patients from Curacao used tolbutamide, while none of Indonesian DM2 patients used it. Differences in the frequency of antidiabetics used, may also explain the differences in results. As reported by Teeuw et al. [38] and Simpson et al. [39], HbA1c levels might be affected by the treatment DM2 patients receive, i.e., both the drugs they use and the periodontal treatment the patients have received. Thus, a drug-related reduction in HbA1c levels in patients not yet adequately periodontally treated might be responsible for the failure of PISA to predict HbA1c levels in our Indonesian DM2. Second, the average BMI of DM2 patients from Curacao was 31 while the average BMI of Indonesian DM2 patients was substantially lower, namely 25. BMI may be an effect modifier, i.e., a higher BMI may increase the potential insulin resistance inducing effect of periodontitis in DM2 patients [40, 41]. Third, there is clear difference in ethnicity between the two groups, i.e., one from Indonesia of Javanese origin and the other from Curacao of African-American origin. Possible differences in (health promoting) behavior, diet, and genes, related to the differences in ethnicity, may be another explanation for the differences in results [42, 43].

## Conclusions

PISA was shown to be a predictor of HbA1c in healthy Indonesians in conjunction with CRP, age, sex, and smoking. This implies that periodontitis might contribute to insulin resistance through the inflammatory and infectious burden leading to DM2. In Indonesian patients, treated for DM2, PISA was not able to predict HbA1c.

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**Conflict of interest** The authors declare that they have no conflict of interest.



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